UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,326	12/05/2001	Stefan Peukert	02481.1759	3330

7590 08/22/2003

Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	10

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/002,326	Applicant(s) PEUKERT ET AL.	
	Examiner Sudhaker B. Patel, D.Sc.Tech.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover she t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *10* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' response paper # 9 dated 7/22/03 is acknowledged. Examiner discussed the matter with applicants to advance the prosecution of this application .See interview summary dated 8/11/03, which is enclosed with this communication.

Claims 1-3,5-18 are pending in this application. Claim 4 is withdrawn from consideration.

Election/Restrictions

1. Applicant's election with traverse of species of Example 23 as recited on page 45 of the specification in Paper No. 7 has been acknowledged in the earlier Office Communication. The traversal is on the ground(s) that this application can be examined as a single piece for allowance. This is not found persuasive because of the various reasons already cited in the earlier Office Action paper # 8 dated 4/23/03.

2. Upon further review and consideration, it is noted that this application consists of working examples1-9, 19,20 12-17, 21-29,33-51,54-67 for Bisaryl combinations consisting of ***Phenyl-pyridine*** of the Formula IV(according to method A or general working procedure, and ***Phenyl-pyrimidine*** combinations for(9 compounds =) Examples 18,10-12,30-32,52,53. The Assays as recited in Table on page 54, reports that out of 9 compounds having Phenyl-Pyrimidine core 3 were found inactive for the test i.e. more than 30 % of 9 compounds included in the testing. The data provided by the applicants will raise additional issues related to activity, and hence enablement for method of use by the groups and compounds yet to be prepared (but already claimed

herein), and combinations other than phenyl-pyridine for which specification remains silent.

Applicants argue that since compounds of claim 1 share substantial structural feature, the Markush groups do not exist. This is not true. As already recited in earlier office communication paper # 8, dated 4/23/03, the generic Formula (I) of claim 1 with variables A1-A8 wherein either one of A1-A8 is N and the rest are CH, CR5 or 2 of A1-A8 are N and the rest are CH, CR5 R3 and may form following combinations:

1). Pyridine-Phenyl or
2). Pyridine-Pyridine;
3). 1,2-diazine-Phenyl or
4). 1,3 diazine-Phenyl or
5). 1,4-diazine-Phenyl or
6). 1,2-diazine-Pyridine or
7). 1,4-diazine-Pyridinel or
8). 1,4-diazine-Pyridine or
9). Various combinations of diazine-diazine rings and other possibilities as per claim 1 and the substituents R1-R4, R30,R31, R5 which may be further substituted by one or more substituents.

These combinations are chemical non-equivalents of each other. Basic combination e.g. Phenyl-pyridine is not equivalent to other combinations as recited above. Even within the a single ring e.g. the 6-membered rings with 2 Nitrogen atoms in 1,2- or 1,3-, or 1,4- positions will provide Pyridazine, Pyrimidine, Pyrazine cores which when coupled with phenyl ring are chemically different combinations, and they are expected to have different physical and chemical properties.

The groups as presented above, are distinct inventions, each from the other because of the following reasons: The compounds of Groups 1-9 are drawn to:

(1). Structurally diverse compounds that are made and used independently of each other;
(2). Compounds are separately classified;
(3) Classes will require separate literature searches;
(4) Compounds are not art recognized equivalents, and additionally,
(5). The groups lack unity of invention(see MPEP 803.02).

Based on above stated data i.e. (1) - (5)., claim 1 also lacks unity of invention.

Therefore, the variables A1-A8 are defined in such a way that it keeps changing the core of the compounds that determines the classification. By changing these values, several patentably distinct and independent compounds are claimed. In order to have unity of invention, the compounds must have " a community of chemical or physical

characteristics" which justify their inclusion in a common group, and such inclusion is not repugnant to principles of scientific classification" In re JONES (CCPA) 74 USPQ 149 (See footenote 2).

The only common structural feature these combinations have are:

1). Bridge –CO-N(R4R3, bridge –CR30R31-NR2T1, and 2). Phenyl ring which are not inventive, patentably distinct, and are not patentable as they are.

Examiner has searched the combination Phenyl-pyridine only. Any additional search within the time made available for through examination of this application will require more time that is burden some to examiner.

The requirement is still deemed proper and is therefore made FINAL.

- ***Rejections maintained:***

Claim Rejections - 35 USC § 112

Rejections made under 35 U.S.C. 112 Para second in the earlier Office Action as stated above are maintained further for the reasons already stated there. Following addition comments also apply for the same.

(1). Claims 1-3,5-8 start with recitation: " A compound of...., but end up with a mixture of any such compounds in any ratio". Correction to:" A compounds of Formula 1 or a pharmaceutically acceptable salt, or stereo isomeric form thereof" is required.

(2). Claims 9,16-18 recite;" A pharmaceutical preparation..". Correction to:"A pharmaceutical composition" is required.

(3). Claims 10-16 are not only drawn to a method of treating, but also to a method of preventing and a method of terminating atrial fibrillation and atrial flutters

which are mediated by K+ channel related activity of the instant compounds. The specification remains silent to clearly and exactly define various diseases, and others which are K+ channel mediated specific diseases. The specification does not indicate which patient has the potential to be afflicted by such a condition and which patient will not be afflicted. Specification does not teach whether certain patient needs prevention of MS or others(diseases) T-cell mediated autoimmune diseases, or CNS related diseases.

(4). Claim 3 ends with "..". Correction is required.

- ***Rejections withdrawn:***

Applicants argument and remarks are considered favorably, and found persuasive for withdrawal of rejections made under 35 U.S.C. 103(a). See allowable subject matter section bellow.

- **Rejections maintained:**

Applicants desired additional details on record for rejections earlier made, and rejections related to enablement under 35 U.S.C. 112 paragraph first. The same are elaborated for applicants' record.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims10-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a disease, does not reasonably provide

enablement for preventing and terminating the diseases or conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

5. The method of use claims is related to diseases or conditions mediated by K+-channel activity. Specification and claims do not exactly define a specific disease. These diseases include diseases related to K+ channel Blockers-Kv 1.3 channels in T cells, and include not only diseases related to Cardiac Channel but also for other diseases, e.g. CNS, MS, neurological diseases, and diseases yet to be discovered. See article by Kath et al as recited bellow.

(1). In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

(2). "Pharmaceutically tolerable salt, in an stereo isomeric form, or a mixture of any such compounds in any ratio "as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carbocyclic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1, (or other claims dependent on it) and/ or its pharmaceutical preparations in its "salt or stereo isomeric form in combination with a pharmaceutically acceptable additives and ***other pharmacological active compounds***". Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their combinations either alone or in a combination therapy as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(I).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

The claims are drawn to compounds, pharmaceutical preparation(s), and method(s)(but not limited to a one definite disease) for their generic use for treating as well as for preventing terminating diseases and conditions as outlined earlier.

1). **The nature of the invention:** The compounds and their method of use claim(s) are drawn in part to use them for the treatment, and preventing or terminating disorders or diseases caused by K+ channel-related activity in a generic way.

2). **The state of prior art:** There are no known compounds of similar structure (i.e. compounds of invention of Group having a chemical combination Phenyl-pyridine which have been demonstrated not only for the treatment of disorders but also for "prevention & terminating" of disease/conditions caused by K+ channel blockers in a generic way.

3). **The predictability or lack thereof in the art:** It is presumed in the use for patient(s) who are animals suffering from disorders or disease caused by activity related to K+channel as claimed herein, there is a way of identifying those patient(s) who may develop any kind of physiological conditions including (but not limited to) a single disease, atrial fibrillation or atrial flutters. There is no evidence of record, which would enable the skilled artisan in the identification of the patient(s) who have the potential of becoming afflicted with the physiological conditions related to activity of K+ channel blockers as claimed herein.

4). **The amount of direction or guidance present and 5).:** The presence or absence of working examples: There are no doses present to direct one to protect a potential host from a K+ channel-related disorder or disease, and other multiples of physiologically related condition(s) of various types.

6). **The breadth of the claims:** The claims are drawn to physiological conditions (not limited to) for treatment or preventing or terminating of disorder or disease caused by a K+channel blocker activity which are not related and whose treatment(s) is unknown by compound of instant invention.

7). **The quantity of experimentation** need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following references are cited to show the present state of art(s):

- **Role of Kv 1.3 during T cell activation:**

Kath et al(Annual Report in Med. Chem. Vol. 32; pages181-190(1997)) state that:" Due to its distinct mechanism and restricted tissue distribution, a Kv 1.3 blocker would not likely display the same toxic side effects of currently used

immunosuppressants such as cyclosporin and FK-506....see page 182 lines 35-38. Authors also state that When tested against a panel of 10 related voltage-gated K+ channels, comparable activity was only observer with Kv1.4(IC50 =0.3), a channel found in heart and brain. See page 185 last 3 lines. Authors further conclude that despite the rapid increase in knowledge regarding lymphocyte ion channels, the field of Kv 1.3 blockers remain immature.. Looking toward the future, further mapping ***of toxin-channel interactions may provide key insights*** into the design of agents suitable for testing in man. See page 188 in section conclusion, last 5 lines ".

- **The effect of (other compounds)second generation histamine antagonists on the heart:**

Grzelewska et al(PubMed Abstract11575008, also cited as Pneumonol. Alergol. Pol.,69/3-4,217-26(2001)). State that:" Fexofenadine- the major metabolite of terfenadine, does not block either HERG or Kv 1.5. The guinea pig model (in vitro) revealed that only terfenadine, astemizole and ebstine produced significant QT interval prolongation and arrhythmogenic effects".

- **Characterization of recombinant HERG K+channel blockade, the class Ia antiarrhythmic drug procainamide:**

Fidley et al (PubMed Abstract 12804575, also cited as Biochem. Biophys. Res. Commun., 306/2,388-93(2003)) state that Thus, differences between the chemical structure of PROC and other Class Ia antiarrhythmic drugs may help to provide insight into chemical determinants of blocking potency for agents that..to open/activated HERG channels".

- **The voltage-gated Kv 1.3 K+ channel; in effector memory T cell as new target for MS:**

Wuff et al(Pub Med Abstract 12782673, also cited as J. Clin. Invest. 111/11,1703-13(2003)) state that:" Selective targeting of Kv 1.3 in T(EM) cells may therefore hold therapeutic promise for MS and other T cell-mediated autoimmune diseases".

- **Kir channels in the CNS:emerging new roles and implications for neurological diseases:**

Neusch et al(PubMed Abstract 12596033, also cited as Cell Tissue Res., 311/2, 131-8,(2003)) state that:" We summarize the in vivo data that demonstrate the role of Kir channels in regulating morphological events, such as the proliferation, differentiation and survival of neurons and glia cells".

- **Importance of Mitochondral K ATP channel in the antiarrhythmic and cardioprotective effects of non-hypotensive doses of nicorandil and cromakalim during ischemica/reperfusion study in an intact anesthetized rabbit model:**

Das et al(PubMed Abstract 12741997, also cited as Pharmacol. Res. 47/6,447-61(2003)) state that:" We, therefore, conclude that intervention by intravenous administration of nicorandil and cromakalin (through the selective activation of mitochondrial K(ATP) channels), increased survival and exhibited antiarrhythmic and cardioprotective effects during coronary occlusion and reperfusion in anesthetized rabbits when administered prior to and during coronary occlusion".

- **The contribution of ionic currents to changes in refractoriness.. human atrial myocytes associated with chronic atrial fibrillation:**

Workman et al(PubMed Abstract 11684070, also cited as Cardiovasc. Res. 52/2,226-35(2001)) state that:" 4-aminopyridine(2 mmol/l) markedly prolonged repolarisation and the ERP(by 35%, $P<0.05$). However, the combination of these drugs(nifedipine & 4-amino-pyridine) had effect on late repolarisation or refractoriness".

In the specification (see pages 53-54), applicants have tried to describe some sort of prior art(s), and assay/testing methods. The results can be summarized in as:

- In Table on page 54, applicants have included compounds of Examples 1-67 without the art recognised reference compounds. Therefore, no direct comparison can be made between the elected species of Example 23 and the art recognized reference.. Additionally, the results consist of range: From Inactive to 0.4 to < 100 reported as IC50 [uM].
- The specification remains silent about the specific method of administration and the also about the dosage-patient regimen.

Therefore, it is difficult to make direct comparison among various data as recited.

Applicants' attention is brought to the fact that the various values reported for above stated test are without involving clinical trials. Applicants have tried to list certain efficacy values obtained by a certain assay method(s), which just indicates a preliminary screening of the compounds prepared. Note, 3 compounds out of 9 having a chemical structural combination "Phenyl-Pyrimidine" tested "INACTIVE" i.e. more than 30% of 9 Examples included in the testing.

There is no demonstration for the ability to prevent diseases as claimed herein by "a process or step of administering to a patient in need of such treatment with an effective amount(dosage) of a compound of generic Formula I of claim 1.

This rejection is applied for:

- the level of unpredictability in the art, and
- the direction for ***prevention*** of diseases provided as to what other aryl substituted rings with different meanings of variables A1-A8 together with additional different meaning for R1-R5, R30,R31 moieties at various locations might work.
-

Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits. The facts provided as above do support the need for additional quantity of experimentation, which would be an undue burden to one skilled artisan in the pharmaceutical arts.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In view of the extreme difficulties that have been and are still being encountered in the prevention of K+channel mediated diseases, such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities. There remains the fact that a single compound, which acts not only for treatment but also for prevention and terminating a disease or condition related to activity of K+-channel, is generally unprecedented. When efforts toward a goal have persistently failed, it is proper for the PTO to require evidence of such a revolutionary result(in re Ferens, 163 USPQ 609). Evidence as recited by the applicants cannot possible demonstrate effectiveness for treatment as well as prevention & termination generally.

Conclusion

Allowable Subject Matter

6. The following is a statement of reasons for the indication of allowable subject matter:

Claims 1-3,5-9 related to subject matter as elected for Phenyl-pyridine combination, would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and others, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The closest prior art ref. of record Kamber et al(U.S.P. 4616002) teaches dihydro pyridine compounds, compositions and utility for treating cardiovascular disorders. See compounds of Formula(I) of abstract, and compounds of claims 1-2 in columns 55-58 wherein Ar = monocyclic aryl or a six membered monocyclic heteroaryl which are phenyl and pyridyl which are substituted by Ac, R2, R3 (in pyridine core), and aryl/pryridine core having alkyl, alkoxy, OH, COOH or, alkoxycarbonyl, carbamoyl, N-loweralkylcarbamoyl.

The instantly claimed compounds differ from Kamber by having the bridge -CO-N(R2)R1) = -CO-NH-CO-O-alkyl. The ref. '002 does teach making of compounds with bridges: -CO-NH-**CH2**-CO-OR7 and bridge -CO-N(R4)(R3) = -CONH-Alkyl = N-loweralkylcarbamoyl.

The other art ref. Mesnard et al(Chemical Abstract DN 84:31261, also cited as Eur. J. Med. Chem. 10/3,315-22(1975)) teaches synthesis and antifibrinolytic properties of some epsilon amino acids. See compounds having CAS RN 57743-15-4. Mensnard differs from the instant compounds by not having Phenyl-pyridine combination.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

Sudhaker B.Patel, D.Sc.Tech.
August 21, 2003.

MUKUND SHAH
SUPERVISORY PATENT EXAMINER
ART UNIT 1624